

***REMARKS/ARGUMENTS******Amendments to the Claims***

The claims have been amended to point out more particularly and distinctly claim the invention. Claim 1 has been amended to recite a method of simultaneously preventing hearing loss of retro-cochlear origin and epileptic seizures. Claims 3 has been amended to recite the prevention of hearing loss, specifically. Claim 4 has been re-written as a dependent claim and to recite the prevention of epileptic seizures, specifically. Claim 2 has been canceled.

***Office Action***

Claims 1-4 have been subjected to a restriction requirement, in which the claims have been grouped as follows: Group I (claims 1-3, drawn to a method of treating or preventing hearing loss) and Group II (claim 4, drawn to a method of preventing epileptic seizures). Claim 4 has been withdrawn.

Claims 2 and 3 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 1-3 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claims 1-3 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nekrassov et al., *Brain Research*, 868, 222-229 (2000) (“Nekrassov et al.”) in view of Woolf et al., *Antimicrobial Agents and Chemotherapy*, 32, 865-872 (1988) (“Woolf et al.”).

***Discussion of the Office Action***

With regard to the restriction requirement, as noted above, claim 1 has been amended to recite a method for simultaneously preventing hearing loss of retro-cochlear origin and epileptic seizures. The present inventors originally contemplated that the prevention exerted by vinpocetine on the changes produced by the models of experimental epilepsy (i.e. PTZ and 4-AP) on both the electrical activity used to monitor the state of audition (ABRs and auditory threshold) and the electrical activity used to monitor the general state of the brain (EEG) were part of a single invention, because one effect is not necessarily linked to the other. The most

widely used antiepileptic drugs, although, like vinpocetine also prevent the changes in the cortical activity (monitored by the EEG) induced in the same animal models of epilepsy, do not prevent the changes in the retro-cochlear waves or the auditory threshold, and rather exacerbated them (see, e.g., Nekrassov et al., *Neuroscience Letters*, , 406: 276-280 (2006); Nekrassov et al., *Clinical Neurophysiology*, 119: 2608-2614 (2008)). The simultaneous prevention exerted by vinpocetine on the parameters linked to audition as well as on those linked to the epileptiform activity accompanying seizures are not taught or suggested by the cited references. The method recited in amended claim 1 is therefore believed to form a single general inventive concept under PCT Rule 13.1, which is believed to overcome the restriction requirement. Accordingly, withdrawal of the restriction requirement is respectfully solicited.

With regard to the rejection as to written description, the Office has alleged that the recitation in claim 3 of “hearing loss of central origin” is not in the specification. In this regard, hearing loss of central origin and hearing loss of retro-cochlear origin are considered to be synonymous. Both expressions mean that hearing loss is not triggered by a damage of peripheral structures such as hair cells or the auditory nerve. Nevertheless, claim 3 has been amended to replace “hearing loss of central origin” with “hearing loss of retro-cochlear origin” which is fully supported by the specification. Claim 2 has been canceled. The amendment of claim 3 and cancelation of claim 2 are believed to overcome the rejection as to written description. Accordingly, withdrawal of the rejection as to written description is respectfully solicited.

With regard to the indefiniteness rejection, the Office has alleged that the effective amount (of drug) recited in claim 1, the “damage” recited in claim 2, and the underlying cause of hearing loss as recited in claim 3, rendered the claims indefinite. Hearing loss induced by seizures in subjects is linked to auditory retro-cochlear tract alterations. The present application shows that the same amount of vinpocetine was sufficient to inhibit auditory tract alterations, hearing loss and seizures. Accordingly, the effective amount of drug as recited amended claim 1 is believed to be clear and definite. Claim 1 also has been amended to clarify that the drug is administered to a subject in need thereof. Additionally, claim 3 has been amended to delete the underlying cause of hearing loss, and claim 2 has been canceled. The amendment of claims 1 and 3, and the cancelation of claim 2, are

therefore believed to overcome the indefiniteness rejection. Accordingly, withdrawal of the indefiniteness rejection is respectfully solicited.

With regard to the obviousness rejection, Applicant respectfully submits that the cited references, alone or in combination, do not disclose or suggest administering vinpocetine in accordance with the claimed method. In the studies disclosed by Nekrassov et al., aminoglycoside antibiotics increased wave I and other waves latencies. Woolf et al. relates to the prevention by an antivirus of the infection (labyrinthitis and hearing loss of peripheral origin) produced by the virus. Taking into account the anatomical proximity of the semicircular channels and the cochlea, a concomitant damage of the cochlear and/or the auditory nerve by the virus accompanied by hearing loss is expected. However, the methods disclosed by Woolf et al. are not analogous to the method recited in the pending claims, which is directed to simultaneously preventing hearing loss of retro-cochlear origin and epileptic seizures by prophylactically administering to a subject in need thereof vinpocetine in an amount sufficient to simultaneously inhibit auditory tract alterations linked to the hearing loss and seizures.

Aminoglycoside antibiotics damage peripheral structures, as shown by the alterations in the first wave (wave 1 in humans or P1 in animals). Auditory evoked potentials are commonly referred as “brainstem auditory evoked potentials (BAEPs)” or “auditory brainstem responses (ABRs),” but this does not mean that all the waves of those potentials originate from nuclei at the brainstem level. Aminoglycoside antibiotics are unable to change directly the physiology of the brainstem retro-cochlear nuclei generating the later ABR waves. Although, the changes resulting from damage of the inner ear function induced by the chronic treatment with the aminoglycoside antibiotics can indirectly affect other ABR waves. In contrast, the acute changes in the later ABR waves linked to epilepsy cannot change indirectly the more peripheral waves (such as wave 1). Therefore, Applicant’s discovery, which shows that vinpocetine simultaneously prevents the hearing loss linked to alterations of the later ABR waves observed during epilepsy, and epileptic seizures, is not disclosed or suggested by Nekrassov et al., alone or in combination with Woolf et al.

As noted previously, a judgment on obviousness may only involve some level of hindsight so long as it does not rely on knowledge gleaned only from an applicant’s disclosure (M.P.E.P. § 2145(X)(A)). In other words, “[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 48

USPQ2d 1321 (Fed. Cir. 1998). Simply stated, “[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.” *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Thus, it is improper to pick and choose from among isolated disclosures in the prior art to arrive at the claimed invention using the benefit of Applicant’s disclosure as a guide, particularly when there is no evidence that anyone prior to Applicant’s discovery had heretofore discovered the claimed method, which the cited art fails to disclose or suggest.

Accordingly, Applicant respectfully submits that the amended claims are not obvious in view of the cited references. For at least the foregoing reasons, withdrawal of the obviousness rejection is respectfully solicited.

*Conclusion*

Applicant respectfully submits that the present application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

  
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Date: June 4, 2010